A STUDY ON ANTIBACTERIAL PROPHYLAXIS AFTER CHEMOTHERAPY FOR BREAST CARCINOMA PATIENTS

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CERTIFICATE

This is to certify that this dissertation titled A Study On Antibacterial Prophylaxis After Chemotherapy For Breast Carcinoma Patients is a bonafide record of work done by **Dr. D. David Praveenkumar** under my guidance during his postgraduate study period between 2008-2011.

This Dissertation is submitted to THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, in Partial fulfillment for the **Degree of Doctorate in Medicine in Branch VII – Medical Oncology**

It has not been submitted (partial or full) for the award of any other degree or diploma.

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CONTENTS

ABBREVIATIONS

ANC – Absolute Neutrophil Count

Chemo RT - Chemoradiotherapy

CMF – Cyclophosphamide, Methotrexate, 5- Flurouracil

DHAP – Dexamethasone, Cytosine- Arabinoside, Cisplatinum

FAC- 5 - Fluro uracil, Adriamycin , Cyclophosphamide

FEC – 5 - Fluro uracil, Epirubicin, Cyclophosphamide

FEC –D - 5 – Flurouracil, Epirubicin, Cyclophosphamide- Docetaxol

FN- Febrile neutropenia

G-CSF – Colony stimulating factor

ICE – Ifhosfamide, Carboplatin, Etoposide

ICU – Intensive Care Unit

LDH – Lactate Dehydrogenase

PS – Performance Status

TMP-SMZ-- trimethoprim–sulfamethoxazole

INTRODUCTION

With the advent of cytotoxic therapy for cancer especially the intensified dose regimens used in haematological cancer and solid tumors, occurrence of febrile neutropenia poses a major problem in treating this patient population. Though fever and infection as a consequence of neutropenia, in cancer patients were first described about 100 years ago still bacterial infections are life threatening complications in patients with severe, persistent neutropenia. Without preventive measures, 48% to 60% of febrile neutropenic patients have an infection, while 16% to 20% of profoundly neutropenic patients (neutrophil counts $<0.1 \times 10^9$ cells/L) develop bacteraemia . Neutropenia leads to increased hospitalisation, increased costs and loss of quality of life. Most dreadful complication of febrile neutropenia is mortality which ranges from 2 to 21% in various studies.[1]

To prevent chemotherapy-related FN, prophylactic antibiotics and granulocyte colony-stimulating factor (G-CSF) have been applied successfully. Earlier Studies evaluating prophylaxis with trimethoprim–sulfamethoxazole (TMP-SMZ) demonstrated a reduced infection rate for patients treated with TMP-SMZ when compared with placebo or no treatment.[1] However with the decreasing efficacy of TMP-SMZ in modern times fluroquinolones have emerged as a good alternative for prophylaxis in febrile neutropenia. When quinolones are used for prevention of infection in neutropenic patients, the rate of Gram-negative bacteraemia is reduced to 1–2%. The advantages of using fluroquinolones are: they are orally absorbable, have broad antimicrobial spectrum and also have some activity against gram positive organisms and it is cost –effective. The main problem with chemoprophylaxis is the emergence of resistance especially to Escherichia coli; however, since the antibiotics

used for chemoprophylaxis in cancer patients are widely used in the community, it is unlikely that their use in neutropenic patients will significantly aggravate the overall situation.[2]

Many drugs in the fluroquinolone group such has ciprofloxacin, moxifloxacin and levofloxacin has been tried as prophylaxis in febrile neutropenia in various studies across the world. Gatifloxacin has not been tried in vivo in the chemoprophylaxis of febrile neutropenia. Also there is a paucity of studies related to the prophylaxis in febrile neutropenia in our country where the disease burden is substantial when compared to the western countries. In this background this study is attempted to assess the clinical evidence supporting the efficacy of antibiotic prophylaxis with fluoroquinolones in neutropenic cancer patients.

AIM OF THE STUDY

- To assess the clinical evidence and impact supporting the efficacy of antibiotic prophylaxis with fluoroquinolones in neutropenic breast carcinoma patients.

REVIEW OF LITERATURE

Definition of febrile neutropenia

- Fever: A single oral temperature of greater than 38.3°C (101°F) or 38.0°C or greater (100.4°F) for over 1 hour.
- Neutropenia: absolute neutrophil count less than 500 mcL or less than 1,000 mcL with predicted rapid decline in 48 hrs.

50% of febrile patients will have no documentation of infection. 20% will have clinically positive infection and 30% have microbiologically (culture positive) documented infection. [3]

Fever is an indicator of infection, even though other causes of fever can be present eg. drug fever or fever due to malignancy itself, blood products etc. However fever due to neutropenia should be considered seriously because infection develops and progresses rapidly in neutropenic patients which sometimes may be fatal .[4]

Incidence of febrile neutropenia in chemotherapy regimens in breast carcinoma patients

On the basis of the regimens used and their reported febrile neutropenia (FN) rates, the incidence of FN among women receiving chemotherapy for node-positive early-stage breast cancer is estimated at around 16%. It is roughly estimated that more than 1000 women in UK who receives chemotherapy for node positive breast cancer will have febrile neutropenia. [5]

PACS trial compared 6 cycles of FEC combination chemotherapy with 3 cycles of FEC followed with Docetaxol. The incidence of grade 3 and 4 neutropenia is 10.9% and 20.2 % in FEC and FEC-D combination chemotherapy respectively where as incidence of FN is 8.4% and 11.2%. . The authors noted that even though docetaxol had higher incidence of FN , most of the episodes occurred only in first cycle .[6]

David et al , conducted a phase II trial where 60 locally advanced breast carcinoma patients received 5 cycles of Taxol- Epirubicin combination neoadjuvant chemotherapy . They reported the incidence of febrile neutropenia as 16%. However no death or life threatening infections was reported.[7]

Moon et al in their study of 82 locally advanced breast cancer patients treated with FAC neoadjuvant chemotherapy where by 5- Flurouracil was given as continous infusion showed the incidence of grade 3 and 4 neutropenia as 36%.One patient had pneumonia with sepsis.[8]

In a randomnised trial , FAC combination chemotherapy was compared with Vinorelbine – Doxorubicin combination in metastatic breast carcinoma patients . The incidence of grade 3\ 4 neutropenia and febrile neutropenia was 7% and 25% respectively in both arms .[9]

Ismaili et al compared 2 groups of breast carcinoma patients who received concurrent chemoradiotherapy as adjuvant therapy. One group received Anthracycline based chemotherapy (FEC-75, FAC-50) and another group CMF combination chemotherapy. Rate of grade 3 and 4 neutropenia was 9.3% and 6.2% respectively and grade 2\3 anemia was also more in the anthracycline arm .[10]

History of febrile neutropenia

First description of febrile neutropenia was given by Bodey and colleagues even before 3 decades. He observed 52 leukemic patients at National Cancer Institute and found out that severe infections occurred when neutrophils count is less than 1000 per cubic mm. He proposed an association between infection, fever and fall in neutrophil counts.[11]

In the management of febrile neutropenia , the scientific basis for doublet antibiotic usage was proposed by Schimpff and colleagues. They observed 75 leukemic patients who had febrile neutropenia. The most common organism isolated from them was Pseudomonas aueruginosa. These patients were treated with empirical antibiotic combination carbenicillin and gentamicin . These patients had better outcome than those patients treated with single agent gentamicin in the same year.[12]

Pizzo and colleagues proposed the role of antifungals by adding Amphotericin-B if neutopenic fever continues more than 7 days. By adding antifungals , mortality and incidence of septic shock drastically decreased. [13]

Risk factors for febrile neutropenia

Risk factors for febrile neutropenia may be patient related, tumour related, treatment related or laboratory abnormalities

Patient related risk factors

Age

Advanced age is a risk factor for severity of neutropenia and its complications. Usually they have comorbids and poor general condition. Their tolerance to chemotherapy is poor. Often elderly aged patients are treated with lesser dose of chemotherapy to minimize chemotherapy related toxicities.[14]

Poor performance status and comorbidities

Poor performance status , comorbidities such as renal, cardiac, liver disease, chronic obstructive pulmonary disease , systemic hypertension , diabetes mellitus has shown in various studies to increase the duration and severity of FN .This can lead to prolonged hospitalisation and death.[15]

Tumour related risk factors

Comparing solid and haematological cancer patients, latter patients have higher risk of neutropenic complications and death, due to the reasons of disease process itself and greater intensity of treatment.[16] In solid malignancies patients with advanced disease are more prone for febrile neutropenia which may be due to poor performance status, bone marrow involvement, immunosuppression etc.[17]

Treatment related risk factors

Another risk factor for febrile neutropenia is the intensity of chemotherapy regimens. Some regimens are more myelosuppressive than others. Eg DHAP, ICE salvage regimens used in Non Hodgkins Lymphoma , BEACOPP regimen in

Hodgkins lymphoma , high dose anthracycline regimens in breast carcinoma patients.[17]

Laboratory Abnormalities

Hemogram and biochemical values may predict the severity of disease, co-morbidities and impact of cytotoxic chemotherapy. If the pre-treatment hemoglobin is less than 12 gm, it predicts severe neutropenia. [18] In another study, patients with non Hodgkins lymphoma treated with CHOP chemotherapy , having pre-treatment albumin of less than 3.5 gm and LDH greater than upper limit of normal served as significant predictors of higher chance of febrile neutropenia.[19]

Risk Models for Predicting Chemotherapy-Induced Neutropenia

For the last 10 years several investigators have identified subset of post chemotherapy patients who are at low risk for febrile neutropenia. These patients can be given outpatient treatment for the febrile episode or early discharge from the hospital so that they can continue treatment in home. Kern et.al and Freifeld et al conducted two large randomised trials and showed efficacy and safety of empirical oral antibiotic (ciprofloxacin and amoxicillin plus clauvulanate) compared with parenteral antibiotic in these low risk patients. [20]

In various studies, definition of low risk is not uniform. To define low risk, Talcott et al conducted a retrospective study, where by 261 medical records of 184 cancer patients were reviewed. He classified them in to 4 groups , out of that 3 groups had significant higher risk than the remaining patient group whom seems to be at lower risk..They proposed patients with no comorbids and controlled cancer are at lower risk with expected medical complications less than 5%. [21]

Multinational Association of Supportive Care in Cancer (MASCC) conducted a prospective study in febrile neutropenic patients to develop a scoring system to identify low risk individuals. Definition of low risk according to MASCC is those having a high probability of fever resolution without development of serious medical complications or death. The following factors such as burden of illness, hypotension, chronic obstructive pulmonary disease, solid tumor or no previous fungal infection in hematologic malignancies, age, outpatient status and dehydration were taken into account. On validation , a MASCC score of ≥ 21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71%. [22]

Grading of neutropenia.

Adverse Event	**Grade 0 (In Cu.mm)**	**Grade I (InCu.mm)**	**Grade II (InCu.mm)**	**Grade III (In Cu.mm)**	**Grade Iv (In Cu.mm)**
Total Count	**WNL**	**< LLN – 3000**	**> 2000- <3000**	**>1000- <2000**	**<1000**
Neutrophil Count	**WNL**	**>1500- >2000**	**>1000- <1500**	**> 500- <1000**	**<500**
Febrile Neutropenia	**0**	**-**	**-**	**Present**	**Life-Threatening Sepsis**

NCI COMMON TOXICITY CRITERIA [22]

Consequences of febrile neutropenia.

Dose Delays and Reductions

Lymann et al in a retrospective study to assess practice patterns of adjuvant chemotherapy for early-stage breast cancer, observed treatment delay of greater than 7 days in 24.9% patients and dose reduction of greater than 15% occurred in 36.5% patients due to neutropenia, About two thirds of patients received relative dose intensity less than 85%. Patient who were at greater risk are obese , older, patients not on primary G-CSF prophylaxis and three drug combination regimens. [23] Bonnadonna et al have estimated that patients who receive less than 65% of their planned dose have been shown to have survival rates similar to those who receive no chemotherapy at all. [24]

Mortality

Most dreadful complication of febrile neutropenia is mortality. Caggiano et al estimated that in febrile neutropenic patients who are hospitalised the mortality ranges from 3.4%-10.5% with overall mortality of 6.8% [25] whereas Smith et al and Herbst et al have shown a range from 2 to 21% .[26] Lyman et al observed that the higher rates are often seen in patients with age related comorbidities, or in patients with poor performance status, patients with advanced cancer and those who are undergoing palliative chemotherapy .The highest mortality rates were observed for lung carcinoma followed by leukemias and then gastric carcinomas. [27]

Hospitalisation due to neutropenia.

In cancer patients, neutropenic hospitalisation is around 7.83 per 1000 individuals . Hematological malignancies constituted the highest number of hospital admission ie. 43 per 1000 individuals with cancer. In solid malignancies, incidence of neutropenic hospitalisation in descending order was seen in cancer of pancreas, lung, ovary and stomach. In breast cancer patients neutropenic hospitalisation is around 4.9% .[28]

Caggiano et al observed that the mean length of hospital stay was 9.2 ± 10.4 days. The average cost of neutropenic hospitalization was $13,372 ± $21,000. As expected leukemia patients had high mean length of hospital stay and cost of neutropenic hospitalisation where as in solid tumours both were highest in gastric carcinoma. They also observed that even though, in solid tumours duration of hospital stay and cost is less than haematological malignancies incidence of mortality is almost the same. Authors concluded by saying neutropenic hospitalisation is a common and expensive condition with associated mortality in approximately 1 in 14 hospitalized cancer patients. Hospitalisation puts patients at risk of developing further complications, such as hospital-acquired infections and thromboembolic events, which add to the overall cost of FN [29,30]

Increased Costs

Moore and Crom have observed that occurrence of febrile neutropenia in patients lead to increased direct and indirect costs to the individual, the health providing system and the national economy. The costs are due to a range of factors, including hospitalization for treatment of FN, significant morbidity and mortality,

financial losses for patients and their families / carers and reduced health-related quality of life .These increased costs also undermine public confidence in cancer services . [31] Holmes et al have reported that in UK, FN imposes a significant burden on National Health Services finances and resources and a single episode is estimated to cost the NHS £3582 which is due to hospitalization, which on average is 6 – 8 days.. Hospital acquired infections and thromboembolic events add to the overall cost of FN.[32]

Quality of Life

Okon et al[33] have observed that development of FN has been indirectly shown to correlate with lower quality-of-life scores and Glaspy et al[34] have shown an an increase in the incidence and severity of chemotherapy-related side effects such as mucositis, abdominal pain and diarrhea, anorexia and fatigue with development of FN. FN also causes disruption of normal life such as childcare and employment leading to financial and social implications for patients and their families.(Moore and Crom) .[31]

STRATEGIES TO PREVENT FEBRILE NEUTROPENIA

1. Modification of the chemotherapy regimen
2. Use of growth factors & maintenance of chemotherapy dose intensity
3. Prophylactic antibiotics

Modification of the chemotherapy regimen

Chemotherapy dose reductions and treatment delays are common practices. Lyman and colleagues reviewed several randomized trials and concluded that a large percentage of patients—approximately half—receive less than half of their initially planned chemotherapy but in practice this strategy reduces the disease free and overall survival benefit.[27]

Use of growth factors

A phase III study conducted by Martin et al analysed the toxicity and health related quality of life of breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and TAC (docetaxel, doxorubicin, cyclophosphamide) with and without primary prophylactic G-CSF (PPG). They evaluated 1047 patients and found that addition of GCSF significantly reduced the incidence of febrile neutropenia. In addition it was found to reduce other side effects of TAC chemotherapy such as grade 2–4 anaemia, asthenia, anorexia, nail disorders, stomatitis, myalgia and dysgeusia.[35]

Jack Webster conducted a pilot study in 19 patients with newly diagnosed breast cancer receiving adjuvant systemic chemotherapy who met criteria for dose reduction or treatment delay due to neutropenia based on a rationale that relatively short courses of G-CSF may reduce the need for a reduction in chemotherapy dose or a delay in treatment for patients at risk for FN, thus permitting administration of full-dose intensity systemic chemotherapy. All the patients received human G-CSF at a dose of 5 µg/kg daily administered subcutaneously in a nonrandomized fashion

beginning seven to 10 days following chemotherapy. The authors found that after initiating G-CSF, chemotherapy doses were reduced in only three patients (16%), and treatment was delayed in six patients (31%) and a significant difference in the proportion of patients experiencing treatment delays was observed ($P<.05$). Also differences in the mean ANC in pre GCSF and post GCSF showed a rising trend with each week of chemotherapy. They concluded that breast cancer patients receiving standard adjunctive chemotherapy who meet criteria for dose reduction or treatment delay can safely continue on full-dose intensity chemotherapy using relatively short courses of G-CSF.[36]

A randomized phase III study investigated the role of the addition of primary G-CSF prophylaxis to primary antibiotic prophylaxis in Small cell lung carcinoma patients who were at risk of FN because of either elderly age, poor performance status, Co- morbid , and / or previous chemotherapy treatment. 175 patients were accrued and randomly assigned for treatment with cyclophosphamide, doxorubicin, and etoposide (CDE), followed by prophylactic antibiotics alone (ciprofloxacin and roxithromycin) or by antibiotics in combination with G-CSF on days 4 to 13. There was a 50% reduction in the incidence of FN in cycle 1 with the addition of GCSF to antibiotics when compared to antibiotics group(10 vs 20 patients respectively , P =0.01). In patients with FN during 1st cycle there was marginal difference between the two groups in regard to the duration of an episode of FN (median, 4 *v* 3 days), the duration of hospital admission for FN (median, 10 *v* 6 days), and the duration of therapeutic antibiotics needed because of FN (median, 7 *v* 8 days). Duration of hospital admission (all causes) in cycle 1 was shorter in the antibiotics plus G-CSF group compared with the antibiotics-only group, due to the difference in incidence of

FN (mean, 5.7 *v* 2.7 days). However it was similar in both groups in cycles 2 -5. The median delivered dose intensity of cyclophosphamide and doxorubicin for cycles actually delivered was statistically significantly higher in the antibiotics plus G-CSF arm, but the absolute difference was only 7.0 and 0.2 mg/m^2/wk, respectively.[37]

Role of antibiotic prophylaxis

Another method to decrease febrile neutropenia is the prophylactic use of antibiotics especially quinolones but there is a concern that it will give rise to the emergence of resistant gram negative organisms. In an attempt to settle the controversy of the role of prophylactic antibacterial agents after chemotherapy , Michael Cullen and his colleagues conducted a randomized, double-blind, placebo-controlled trial in 1565 patients who were receiving cyclic chemotherapy for solid tumors such as breast cancer, lung cancer, testicular cancer or lymphoma and who were at risk for temporary, severe neutropenia (fewer than 500 neutrophils per cubic millimeter).Patients were randomly given levofloxacin 500mg once daily or a placebo for the seven days during the expected neutropenic period. The primary outcome was the incidence of clinically documented febrile episodes (temperature of more than 38°C) attributed to infection.

The authors observed that during the first cycle of chemotherapy and the entire course of chemotherapy less percentage of patients in levofloxacin group had documented febrile episodes than the patients in the placebo group. Also the occurrence of probable infection and also the severe infection was less in levofloxacin group when compared with the placebo group. In addition hospitalization was required for the treatment of infection less often in levofloxacin

group. Thus the authors concluded that among patients receiving chemotherapy for solid tumors or lymphoma, the prophylactic use of levofloxacin reduces the incidence of fever, probable infection, and hospitalization. [38]

Antibiotic prophylaxis to cover gram positive organisms

With the increased use of quinolones and intense dose chemotherapy which leads to severe mucositis , there was higher incidence of gram positive infections. It contributed to 20 – 30% of episodes of febrile neutropenia. [39] Various agents such as penicillin, macrolides and vancomycin which are active against gram positive organisms were used for prophylaxis with positive results. [40]

EORTC conducted a double-blind placebo-controlled phase III study in which patients with small cell lung cancer were given standard dose CDE or intensified CDE chemotherapy and were also randomized to receive prophylactic antibiotics (ciprofloxacin 750 mg plus roxithromycin 150 mg, bid, days 4-13) or a placebo. The incidence of febrile neutropenia during the first cycle and through all the cycles were less in the antibiotics arm than in the placebo arm .(11% vs 25% in 1st cycle and 24% vs 43% in all cycles). There were less Gram-positive (12 vs. 4), Gram-negative (20 vs. 5) and clinically documented (38 vs. 15) infections in the antibiotics arm which was attributed to quinolones group and macrolide group of antibiotic. The days of hospitalization was reduced and thus the use of therapeutic antibiotics in the antibiotic arm when compared to the placebo group. However, the overall number of days of hospitalization was not reduced *(P = 0.05*). Death due to infection occurred only in the placebo arm: 6% of all placebo patients vs. 0% of antibiotic arm patients *(P* = 0.022) representing 10% of placebo patients who developed fever. However patients in the antibiotic arm suffered from the adverse

effects of the drug such as grade 2-3 nausea, mucositis and diarrhoea. Thus the authors concluded that prophylactic ciprofloxacin plus roxithromycin during CDE chemotherapy reduced the incidence of febrile neutropenia, the number of infections, the use of therapeutic antibiotics and hospitalizations due to febrile neutropenia by approximately 50% with reduced number of infectious deaths.[41]

Emergence of resistant gram negative bacteremia.

One of the most potential complication of quinolone prophylaxis is the emergence of resistant gram negative infections. Giampaola et al conducted a trial in Italy involving 35 centers with 760 patients randomnised to levofloxacin and placebo. They noted that antibiotic prophylaxis had substantially reduced the incidence of febrile neutropenia. However there was 3% incidence of levofloxacin resistant gram negative bacilli in antibiotic group when compared with 1% incidence in placebo group.[42] Michael and his associates , in a span of four years observed 35 episodes of Escherichia coli bacteremia in a series of 230 cases of bacteremia in neutropenic patients with cancer of which thirteen episodes (37%) were due to quinolone-resistant strains. They also identified that prophylaxis with norfloxacin was the only factor which was significantly associated with the development of quinolone-resistant E. coli bacteremia as all the 13 patients with bacteremia due to resistant strains received norfloxacin ($P < .001$). They concluded that cancer patients with febrile neutropenia may be at risk of developing E.coli bacteremia due to quinolone resistant strain when given fluroquinolone prophylaxis.[43]

Reuter et al conducted a prospective study by discontinuing quinolone prophylaxis and studied the incidence of febrile neutropenia , bacteraemia and

mortality in patients with neutropenia after chemotherapy. The study was stopped prematurely since there was higher incidence of febrile episodes and mortality. They also noticed more gram negative bacteraemia in discontinuation phase than base line. Once the antibiotic prophylaxis was introduced the number of febrile episodes , bacteraemia and mortality came down. [44]

Choice of drug

Gafter –gvili et al conducted a metanalysis on antibiotic prophylaxis in neutropenic patients . They identified 95 trials performed between 1973-1994. Out of these 95 trials, 52 trials used quinolone prophylaxis and 10 trials compared quinolones with trimethoprim- sulfhamethoxazole. Febrile episodes, bacteraemia and mortality were similar in both groups. Indirect comparison of quinolone prophylaxis with placebo, showed a relative risk of 0.62 for all cause mortality where as it was 0.71 when trimethoprim- sulfamethoxazole was compared with placebo. Norfloxacin was compared with placebo in 4 trials and no benefit was reported for mortality but Ciprofloxacin on comparison with no treatment in 6 trials showed all cause reduction of mortality.[45]

Von Baum and his associates conducted a controlled before and after observational study with moxifloxacin prophylaxis in hemato-oncological patients. They compared this data with two periods of levofloxacin prophylaxis ie one a preceding period and another post-observational period. They observed a higher incidence of gram negative bacteremia per neutropenic episode especially due to enterococci with moxifloxacin prophylaxis(11%) when compared with levofloxacin prophylaxis(6%).In patients who received moxifloxacin prophylaxis , 26 out of 30 (87%) Gram negative bacteremias were caused by E.coli which were all

fluroquinolone resistant. With levofloxacin prophylaxis 14 out of 22 (64%) Gram-negative bacteraemias in period 1 and 3 out of 3 Gram –negative bacteremias in period 3 were caused by *E. coli*, all of these being fluoroquinolone resistant. Also a higher incidence of Clostridium difficle associated diarrhoea (43 cases) with an incidence of 33% per neutropenic episode was seen which was significantly higher than with prophylaxis with levofloxacin (6% for period 1, and 13% for period 3). They concluded that though newer fluroquinolones has high activity against anaerobes all fluroquinolones may not be equally beneficial in different therapeutic settings .Thus caution is required when choosing fluroquinolones for prophylaxis in neutropenic patients.[46]

Marc Gurwith and his colleagues from USA conducted a trial in which they observed a reduction in the incidence of fever, parenteral antibiotic usage, and infections with gram-negative bacteria in hospitalized patients with neutropenia with administration of prophylactic trimethoprim – sulfamethoxazole (TMP –SMZ). They also observed that when antibiotics given prophylactically to adults had fewer hospitalizations for infection than the control group who were given placebo only when hospitalized. In children with acute leukemia, TMP-SMZ was effective in preventing bacterial and *Pneumocystis carinii* infections. Though prophylactic TMP and TMP-SMZ had equal efficacy and incidence of side effects, TMP was less effective in suppressing gastrointestinal flora including TMP resistant gram negative rods and infections caused by Pneumocystitis carinii. [47]

Hospitalisation and antibiotic prophylaxis

Cullen et al in their study on antibiotic prophylaxis with levofloxacin in solid tumours and lymphoma had mentioned significant reduction in hospitalisation with

antibiotic prophylaxis. Benefit was more in first cycle when compared with other cycles ie., risk reduction of hospitalisation is 36% in first cycle against 27% across all cycles. Authors had shown prevention of 6 hospitalisations in each cycle when prophylaxis was given to 100 patients. [38]

Heijnen et al , on using roxithromycin and ciprofloxacin as prophylaxis in small cell lung carcinoma against placebo had shown the incidence of hospitalisation was 17% and 31% respectively. In this study intensified CDE combination chemotherapy was used. Also median days of hospital admission was significantly less in antibiotic group when compared with placebo ie., 4 vs 5 days. 2% of patients in antibiotic group and 5% of patients in placebo group required intensive care support. Median days of admission in ICU was 2 and 7 days respectively.[41]

Mortality and antibiotic prophylaxis.

Gafter et al carried out a meta-analysis to find out whether antibiotic prophylaxis in neutropenic patients had any effect on decreasing the mortality. 92 trials were considered which met the inclusion criteria. Out of these 92 trials, 52 trials had quinolone only prophylaxis. These trials include patients with both haematological and solid malignancies. They found out quinolone prophylaxis significantly decreases infection related and all cause mortality. Benefit of quinolone prophylaxis also extends in decreasing the episodes of febrile neutropenia, clinically \ microbiologically documented infections and bacteraemia. Number of fungal infections also did not differ between both the prophylaxis and placebo group.[45]

Mario et al conducted a meta analysis in which quinolones alone against quinlones with additional gram positive covering antibiotics were compared. 9 randomised trials which met the selection criteria were selected. They found out that doublet antibiotic regimen would have benefit in decreasing the number of febrile episodes but however they had no effect on decreasing clinical documented infection and mortality. There were more side effects with combination antibiotics than with single agent quinolones. Since there was no clear cut benefit with gram positive coverage, authors were against the routine use of this strategy.[48]

In his meta-analysis, which consist of 2 parts , Reuel et al compared quinolone prophylaxis with control (placebo, non absorbable antibiotic , co-trimoxazole) in first part and in second part gram positive coverage plus quinolone prophylaxis was compared with controls. They concluded that both these methods had no effect on decreasing the mortality.[49]

Role of Gatifloxacin in febrile neutropenia

In febrile neutropenia, gatifloxacin was used as a monotherapy in the treatment of low risk patients. Rolston et al conducted a study in which eligible 40 adult low risk (breast cancer, sarcoma) febrile neutropenia patients were started on oral gatifloxacin monotherapy. 95% of study population showed response to therapy. The mean time to defervescence of fever was around 4 days. Mean duration of usage of antibiotic was 7 days.[50]

Petrilli et al conducted a study in febrile neutropenic patients falling in the age group range of 3-21years and having solid and haematological malignancies undergoing gatifloxacin monotherapy. Study involved 108 patients with 210

episodes. Nearly 75% had successful treatment. The mean duration of fever and antibiotic usage was 2.4 and 8.1 days respectively. No death was observed in the study. Authors concluded that gatifloxacin was an effective option in pediatric low risk febrile neutropenia patients.[51] Hence gatifloxacin is used in the treatment of low risk febrile neutropenia especially in out- patient setting.

Infections in febrile neutropenia

Cullen et al had documented the foci of infection in the following sites in descending order: upper respiratory tract (24.1%) , lower respiratory tract (12.9%), skin and soft tissue (10.5%) , urinary tract (8.3%) and gastrointestinal tract (4.4%). Severe infections as defined by the authors as severe sepsis related syndrome , death or both was observed in 1% and 2% of patients in Levofloxacin and placebo group respectively.

The microbiologically documented infections in this study were less in antibiotic group when compared with placebo group (4.6% vs 12.6%). Bacteraemia was documented in 2.3% and 3.8%.[38]

Heijhen et al in their study on the prophylactic role of antibiotics by using Ciprofloxacin and Roxithromycin documented clinically ,infections in 15 patients in antibiotic group and 35 in placebo group where as microbiologically documented infections was in 9 and 32 patients respectively. Respiratory and urinary tract infections was documented less in antibiotics group. [41]

Gafter et al in their meta-analysis on studying the role of prophylactic antibiotics in reducing the infection associated mortality had documented lesser bacteraemia, clinically \ microbiologically documented infections, gram positive and negative infections with prophylactic antibiotics.[45]

METHODOLOGY

- 188 breast carcinoma patients were randomly assigned to treatment or observation group each consisting of 94 patients after informed consent. Study period was between October 2009 – November 2010 .
- Patients were stratified according to age (less than 50 years, 50 years or older) , whether they receive concurrent chemoradiotherapy or not and metastatic or non-metastatic disease.
- Treatment group patients received Gatifloxacin 400 mg OD from day 6 to day 14 of each chemotherapy cycle**.**
- When febrile neutropenia occurred , no chemotherapy dose compromise in next cycle was allowed except in patients complicated by life threatening infections.
- Definition of Febrile neutropenia- A single oral temperature of greater than 38.3°C (101°F) or 38.0°C or greater (100.4°F) for over 1 hour with ANC less than 500 mcL or less than 1,000 mcL with predicted rapid decline.
- All febrile neutropenic patients were admitted in the hospital and started on broad spectrum antibiotics according to hospital protocol.
- Decision on oral or IV antibiotic was decided by the treating physician based on age, PS, and clinical picture. It was continued till all signs of infection and fever disappeared.

- For all admitted patients chest Xray and blood culture was done. Total count \ Absolute Neutrophil count was done daily till the count is non neutropenic.
- Admitted patients were discharged from the hospital if afebrile for 2 days , no active infection or ANC > 500.
- Decision on growth factors were taken by the discretion of treating phycisian on the basis of age, comorbids , severity of infection etc
- Severe infection is defined as sepsis related syndrome , pneumonia, hypotension or death.

PATIENT SELECTION

INCLUSION CRITERIA

- Age > 20 years & < 70 years
- PS – 0,1
- Histologically proven invasive breast carcinoma.
- Chemotherapy regimens

  Breast carcinoma – FEC (5-Flurouracil, Epirubicin,Cyclophosphamide), TE (Taxol, Epirubicin) with or with out concurrent radiotherapy (40 gy)

EXCLUSION CRITERIA

- Poor Performance Status (2, 3, 4)
- Compromised renal, hepatic, cardiac function.
- Pancytopenia due to bone marrow involvement.
- Active infection / current antibacterial therapy.
- Cerebral metastases.
- Previous malignancy.
- H/O epilepsy, uncontrolled Diabetis Mellitus.
- Hemoglobin < 10 gm \ dl,. Total count < 4000.
- H/O adverse reactions to Quinolones .
- Previous chemotherapy / Radiotherapy

- Pregnancy and breast feeding.

All patients had hemogram , renal function test (blood urea , serum creatinine) , liver function test (serum bilirubin, SGOT, SGPT, ALP) , chest Xray, ECG, ECHO, US abdomen.

PRIMARY END POINTS OF THE STUDY

- Number of febrile episodes.
- Documented infection.
- Culture positive infection.
- Infection related mortality **.**

SECONDARY END POINTS OF THE STUDY

- Number of febrile episodes in first and then subsequent cycles.
- Days of hospitalisation .
- ICU admissions.
- Requirement of intravenous antibiotics.
- Isolation of organisms
- Whether antibiotic prophylaxis was helpful in elderly or patients with comorbids.

STATISTICAL METHODS

1. Chi- square test of association and Z test of two proportions was employed to test the significance of incidence of febrile neutropenia and to compare it with various parameters like type of chemotherapy used, co-morbids, elderly age, metastatic disease, usage of antibiotics, hospitalisation infections and concurrent chemoradiotherapy.
2. Randomnisation of patients into 2 groups such as arm A who receive Oral Gatifloxacin as antibiotic prophylaxis and arm B who did not receive any antibiotic prophylaxis was done using computerised minimisation algorithm.
3. A sample size of 200 patients was required to demonstrate a absolute decrease in the risk of febrile neutropenia by 20% when patients are treated with prophylactic Gatifloxacin with the statistical power of 80%.

Risk Categorization of febrile neutropenic patients according to cancer institute protocol.

Low Risk

- Solid malignancy
- Age < 60 years
- No comorbid illness
- No organ dysfunction

Intermediate Risk

- Solid malignancy with organ dysfunction
- Age > 60 years
- All hematological malignancies excluding AML/transplant patients

High Risk

- All transplant patients
- AML induction

Therapy :

Our current department policy recommends the following antibiotic(s) as emperic treatment according to risk categorisation prior to availability of the culture and sensitivity report :

Low Risk

Levofloxacin + Co-Amoxy Clavulanate

Intermediate Risk

I line - Cefaperazone / Sulbactam+Amikacin

II line - Piperacillin / Tazobactam

III line - Meropenem / Imipenem

High Risk

I line - Piperacillin / tazobactam

II line - Meropenam \ imipenam

Vancomycin / Teicoplanin included in Staphylococcus aureus infection suspected. If fever persist more than 4 to 5 days, then antifungals are considered.

Gatifloxacin.

- It is a 8- Methoxy Fluroquinolone.
- It belongs to fourth generation quinolone family similar to Levofloxacin.
- It inhibits DNA gyrase or Topoisomerase IV.
- Absorbed well by the gastrointestinal tract with 96% bioavailability. It undergoes limited biotransformation and well distributed in the body. 70% of drug is excreted unchanged in the urine.
- Available in tablet, injection and ophthalmic solution forms
- Oral dosage is 400 mg \ day.
- Side effects- nausea, vomiting , diarrhea, vaginitis, dizziness, hyperglycemia, hypoglycemia, seizures, hallucinations, QT-prolongation syndrome.
- Significant drug interactions occurs with Digoxin, Calcium carbonate, Warfarin, Theophylline, Anti Diabetic agents, Probenecid, Non steroidal anti inflammatory drugs.
- It is one of the antibiotic used as monotherapy in low risk febrile neutropenia patients.

RESULTS

A total of 188 breast carcinoma who met both inclusion and exclusion criteria were randomly assigned to treatment or observation group each consisting of 94 patients between November 2009- October 2010

TABLE 1

Base line characteristics of the patient

	ARM A (AB)	ARM B (no AB)
AGE		
< 50	**51(54.2%)**	**53(56.3%)**
>50	**43(45.7%)**	**41(43.7%)**
RANGE	**25-68**	**29-68**
PS-0,1	**94(100%)**	**94(100%)**
PS-2-4	**0**	**0**
Chemotherapy **FEC** **Taxol\Epirubicin**	 **81(86.1%)** **13(13.9%)**	 **84(89.3%)** **10(10.7%)**
Concurrent RT		
Yes	**53(56.3%)**	**51(54.2%)**
No	**41(43.7%)**	**43(45.7%)**
Stage		
Metastatic	**11(10.8%)**	**8(8.6%)**
Non- Metastatic	**83(88.2%)**	**86(91.4%)**

Co-Morbids		
HT	**18(19.1%)**	**19(20.2%)**
DM	**7 (7.4%%)**	**9(9.5%)**
IHD	**5 (5.3%)**	**1(1%)**

Of the 94 patients in the antibiotic arm, 51(54.2%) patients were less than 50 years of age and 43(45.7%) were above 50 years of age and in the control group which did not receive antibiotics group almost similar distribution was seen where 53 (56.3%) patients were less than 50 years of age and 41(43.7%) of them were above 50 years of age. The range was almost similar in both the groups ie 25 -68 in the antibiotics group and 29 -68 in the control group.

All the patients in both the groups had performance status of 0 -1.

Two types of chemotherapy were employed according to the needs of the patients. In the antibiotics group 81(86.1%) patients received FEC chemotherapy whereas 13(13.9%) patients received taxol / epirubicin. Similar pattern was seen in the control group where 84(89.3%) patients received FEC chemotherapy and 10 (10.7%) patients received taxol / epirubicin chemotherapy.

As the sample is derived from a heterogenous population, concurrent radiotherapy was given to 53 (56.3%) patients in the antibiotic group and 51 (54.2%) patients in the control group. The remaining patients in both the groups did not receive concurrent radiotherapy.

Majority of the patients ie 83 (88.2%) patients in the antibiotic group and 86 (91.4%) patients in the control group had non –metastatic disease. Only 11(10.8%)

patients in the antibiotic group and 8 (8.6%) patients in the control group had metastatic disease.

The incidence of co-morbids such as hypertension and diabetes mellitus were almost similar in both the groups 18(19.1%) vs `19(20.2%) and 7(7.4%) vs 9(9.5%) respectively. However Ischemic heart disease (IHD) was seen in 5 (5.3%) patients in the antibiotic group whereas only 1 patient had IHD in the control group.

TABLE 2

Incidence of Febrile neutropenia

Febrile Neutropenia	**Arm A (Ab)**	**Arm B (No Ab)**	**P Value**
In first cycle (94 cycles)	5(5.31%)	15(15.95%)	0.031 (significant)
In 2-6 cycles (470 cycles)	13(2.76%)	26(5.53%)	0.048 (significant)
In all cycles (564)	18(3.19%)	41(7.26%)	0.04 (significant)

Incidence of neutropenia in the first cycle was seen three times more in the control group than the antibiotic group as 15 episodes(15.95%) occurred in the control group when compared to 5 episodes (5.31%) in the antibiotic group. However in the subsequent 2nd to 6 cycles of chemotherapy 26 (5.53) episodes of febrile neutropenia were observed in the control group compared to 13 (2.76%) episodes in the antibiotic group. Total episodes of febrile neutropenia was also

almost two times higher in patients in the control group than patients in the antibiotic group (41 vs 18). All these observations were found to be statistically significant.

TABLE 3

Chemotherapy and febrile neutropenia

FEC CHEMOTHERAPY

	ARM A (AB)	**ARM B (no AB)**	**p value**
No. of patients	81	84	
No. cycles received	486	504	P=0.05
FN episodes	14(2.88%)	39(7.73%)	(Significant)

In the antibiotics group 81(86.1%) patients received FEC chemotherapy (486 cycles) and 84(89.3%) patients received FEC chemotherapy (504 cycles) in the control group. Incidence of febrile neutropenia was seen less in antibiotics group ie 14 episodes (2.88%) compared to 39 episodes (7.73%) in the control group which was statistically significant.(P = 0.05)

TAXOL / EPIRUBICIN

	ARM A (AB)	**ARM B (no AB)**	**p value**
No. of patients	13	10	
No. cycles received	78	60	P=0.69
FN episodes observed	4(5.12%)	2(3.33)	(Not Significant)

13 patients received taxol/epirubicin in the antibiotics group whereas 10 patients received in the control group. Here slightly more incidence of febrile

neutropenia was seen in antibiotics group than in control group (4 episodes (5.12%) vs 2 episodes(3.33%).However this result was not statistically significant.

TABLE 4

Comorbids and febrile neutropenia

	ARM A (AB)	**ARM B (no AB)**	**p value**
No. of patients	30	29	1.0 (Not significant)
No. cycles received	180	174	
FN episodes	6 (3.33%)	6 (3.4%)	

Similar number of patients had comorbid disease in both the antibiotic group and control group (30 vs 29 patients) and incidence of febrile neutropenia was also the same in both the groups with 6 episodes in each group which was not statistically significant.

TABLE 5

Concurrent RT \ CT and febrile neutropenia

	ARM A (AB)	**ARM B (no AB)**	**p value**
Received RT	53	51	0.1 (not significant)
No. cycles received	318	306	
Had FN	15(4.71%)	25(8.16%)	

Though almost similar number of patients underwent concurrent CT/RT in antibiotics group and control group (53 vs 51 patients) incidence of febrile neutropenia was higher by 1.5 times in the control group than antibiotics group

(15 (4.71%) episodes vs 25 (8.16%) episodes).However it was not statistically significant.

TABLE 6

Metastatatic disease and febrile neutropenia

Febrile Neutropenia	**ARM A (AB)**	**ARM B (no AB)**	**p value**
Metastatic disease	11	8	0.07 (Not significant)
No. cycles received	66	48	
Had FN	1(1.51%)	3(6.2%)	

11 patients in the antibiotic group and 8 patients in the control group had metastatic disease. 1 episode of febrile neutropenia was observed in the 66 cycles of chemotherapy given to patients in antibiotic group whereas 3 episodes of febrile neutropenia was seen in 48 episodes of chemotherapy given to the control group patients which was also not statistically significant

TABLE 7

Hospitalization due to febrile neutropenia

No. of hospitalization	**ARM A (AB)**	**ARM B (no AB)**	**P value**
In first cycle	5	15	0.031
In 2-6 cycles	13	26	0.048
In all cycles	18	41	0.04
Median Duration of Admission (in days)	5	5	-

In first cycle	5	5	
In 2-6 cycles	5	5	
ICU Admission	1	4	0.07(not significant)

Incidence of patients requiring hospitalization in first cycle was three times higher in the control group when compared with hospitalisation in antibiotics group which was statistically significant (15 vs 5). In the subsequent cycles incidence of febrile neutropenia was double the time more in the control group than the antibiotic group (26 vs 13) . Total incidences of hospitalization were also higher in the control group than the antibiotic group (18 vs 41) which was statistically significant. One patient had life threatening diarrhoea and three more patients had pneumonia requiring ICU admission in placebo group where as only one patient in antibiotic group had admission in ICU for pneumonia which was also not statistically significant.

However the median duration of hospitalization remained the same ie 5 days in both the control group and antibiotic group during the 1st cycle and the subsequent cycles of chemotherapy.

TABLE 8

Frequency of Antibiotic Usage

Frequency of AB usage	**ARM A (AB)**	**ARM B (no AB)**	
In first cycle			
Oral AB	2	4	
IV AB	3	11	
In 2-6 cycles			
Oral AB	5	10	
IV AB	8	16	
Median usage(in days)	5	5	
Total Frequency of IV AB usage (564 cycles)	11	27	P value 0.0078 Significant

In the first cycle of chemotherapy 2 patients in the antibiotic group and 4 patients in the control group were given oral antibiotics while 11 patients in the control group were administered intravenous antibiotics and 3 patients in the antibiotic group were administered IV antibiotics.

In the subsequent cycles 5 patients were given oral antibiotics in the antibiotic group as compared to 10 patients in the control group. However 8 patients in the antibiotic group required intravenous antibiotics when compared to 16 patients in the control group requiring intravenous antibiotics.

However the median duration of antibiotic usage remained the same in both the groups ie 5 days. Total frequency of intravenous antibiotic usage remained higher in control group than the antibiotic group (27 vs 11).

TABLE 9

Clinically documented infection (Probable)

	ARM A (AB)	**ARM B (no AB)**
Mucositis (grade III)	3	4
Respiratory tract infection	3	6
Diarrhoea	2	3
IV cannula infection	1	2
Total	9(50%)	15(36.5%)

Grade III mucositis and diarrhoea was seen almost similar in the antibiotic and control group (3 vs 4 and 2 vs 3 respectively).But respiratory tract infection and IV cannula infection were two times more common in the control group when compared with antibiotic group.(6 vs 3 and 2 vs 1 respectively). The observed incidence of clinically documented infection is more in antibiotic group than in observational group (50% vs 36.5%).

TABLE 10

Blood culture positivity documented in febrile neutropenic episodes.

ARM A (16.6%) Of 18 episodes	ARM B (9.7%) Of 41 episodes
Klebsiella pneumonia -1 Esherichia coli -1 Streptococcus pyogenes- 1	Streptococcus pyogenes- 2 Pseudomonas aeruginosa -1 Klebsiella pneumonia- 1

Blood culture positivity of organisms was seen in 16.6% and 9.7% of febrile neutropenic episodes in antibiotic and placebo groups respectively. Klebsiella pneumonia was found in one patient each in both groups whereas Streptococcus pyogenes was seen in 1 patient in antibiotic group and in 2 patients in the control group. Additionally Escherichia coli was seen only in the antibiotic group and Pseudomonas aeruginosa was seen exclusively only in the control group in one patients each. Out of 188 treated patients 1 patient developed hypoglycaemia and 2 patients developed hyperglycemia as a result of gatifloxacin toxicity.

RESULTS

Figure 1 :Incidence of febrile neutropenia

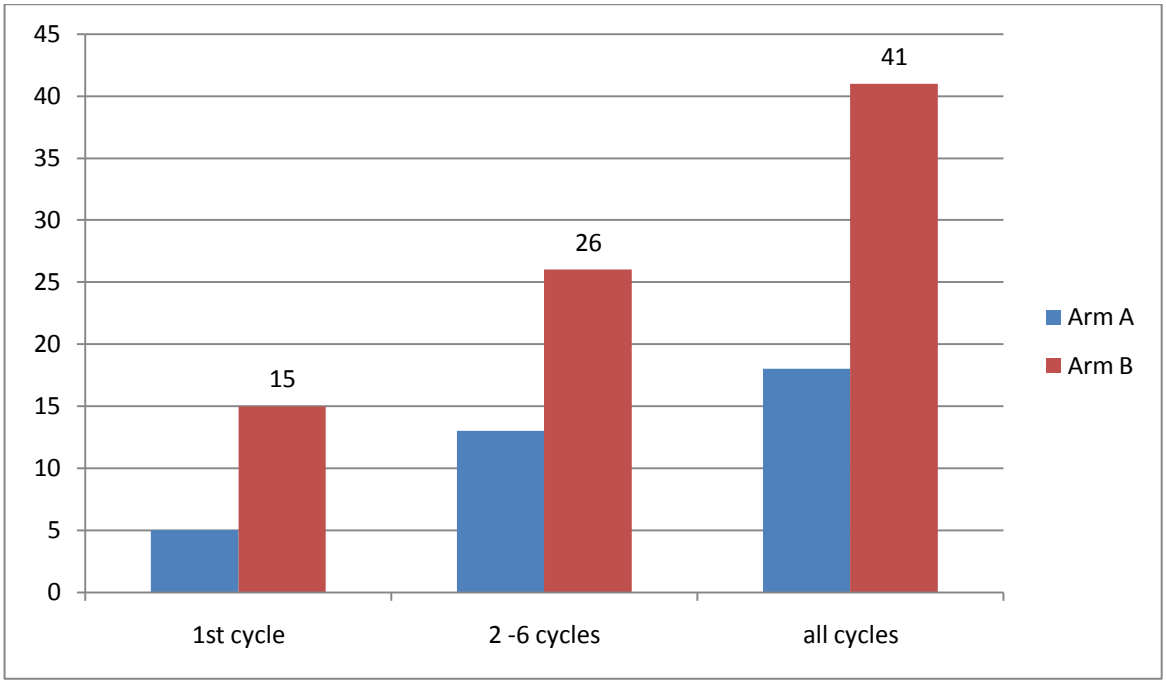


Figure 2 : FEC Chemotherapy and febrile neutropenia

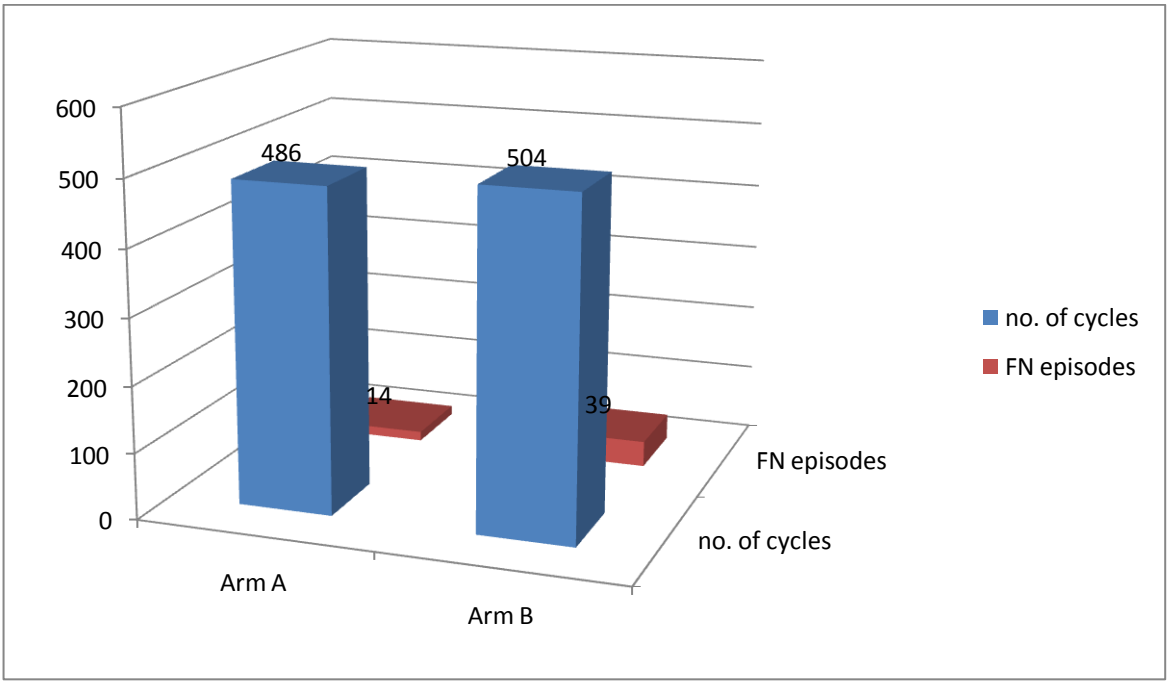


Figure 3 : TAXOL / EPIRUBICIN Chemotherapy And Febrile Neutropenia

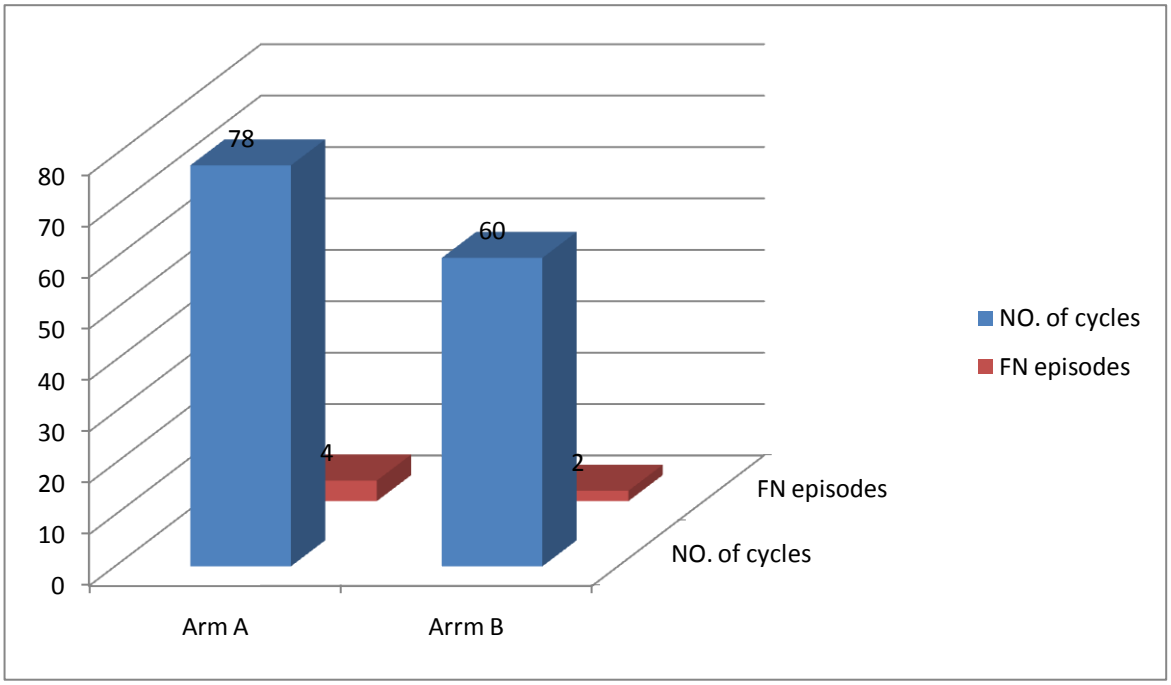


Figure 4 : Comorbids and febrile neutropenia

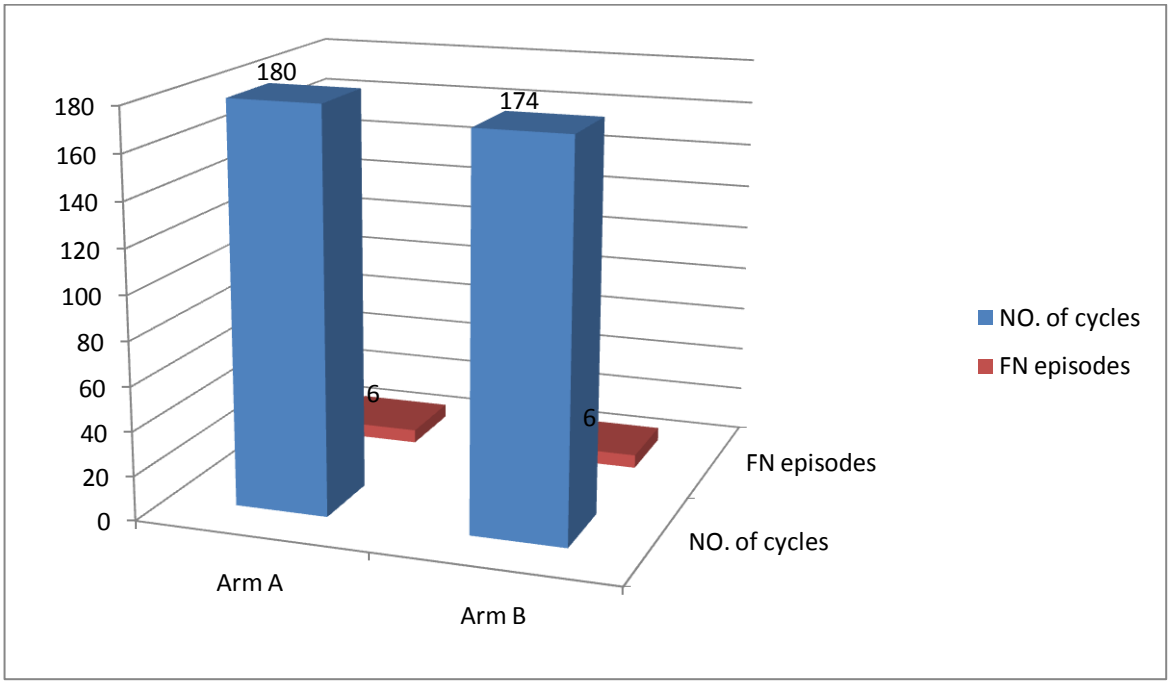


Figure 5 : Concurrent RT \ CT and febrile neutropenia

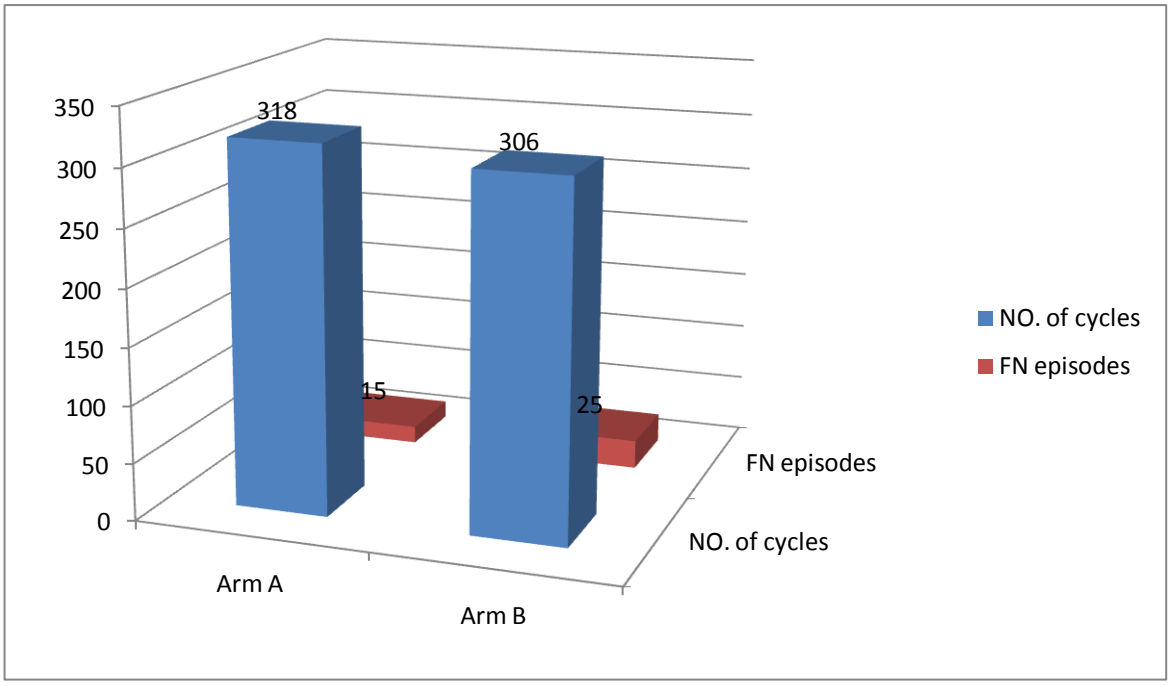


Figure 6 : Metastatatic disease and febrile neutropenia

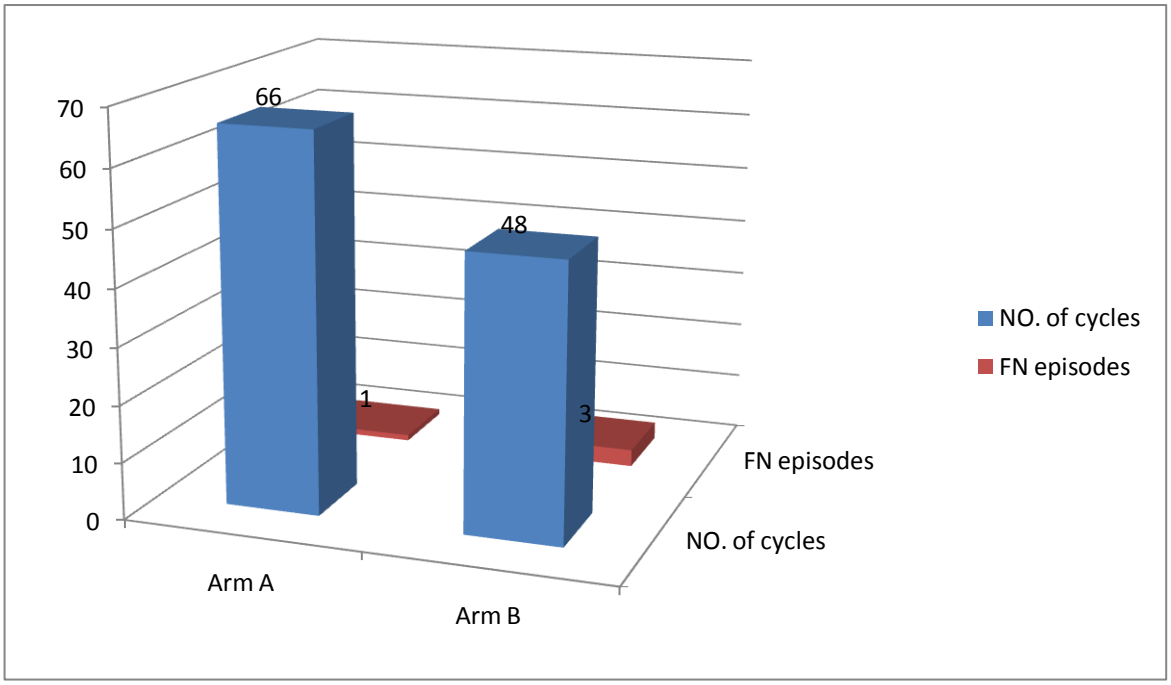


Figure 7 : Frequency of Antibiotic Usage

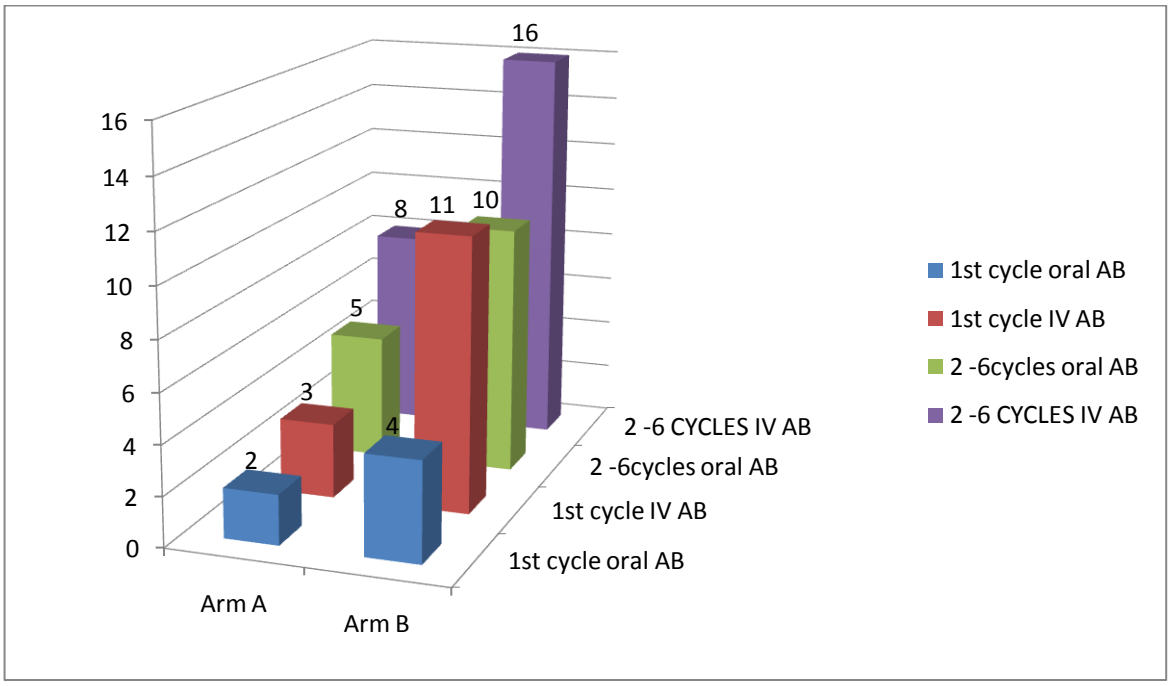


Figure 7 A :Total Frequency Of IV Antibiotic Usage

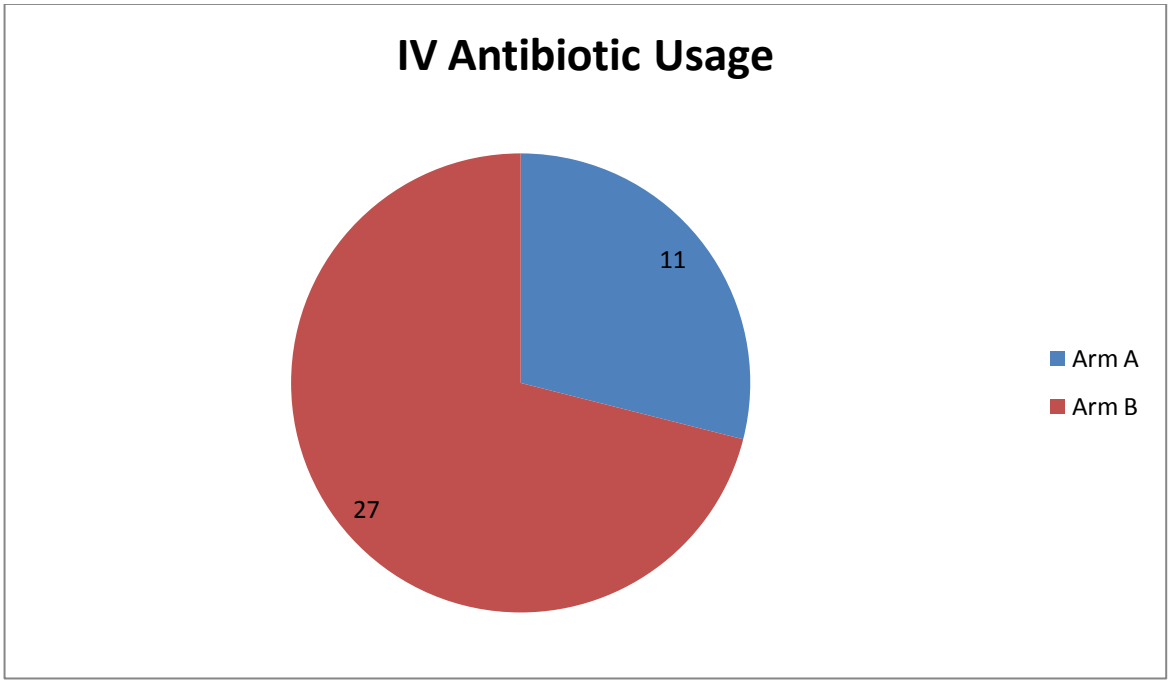
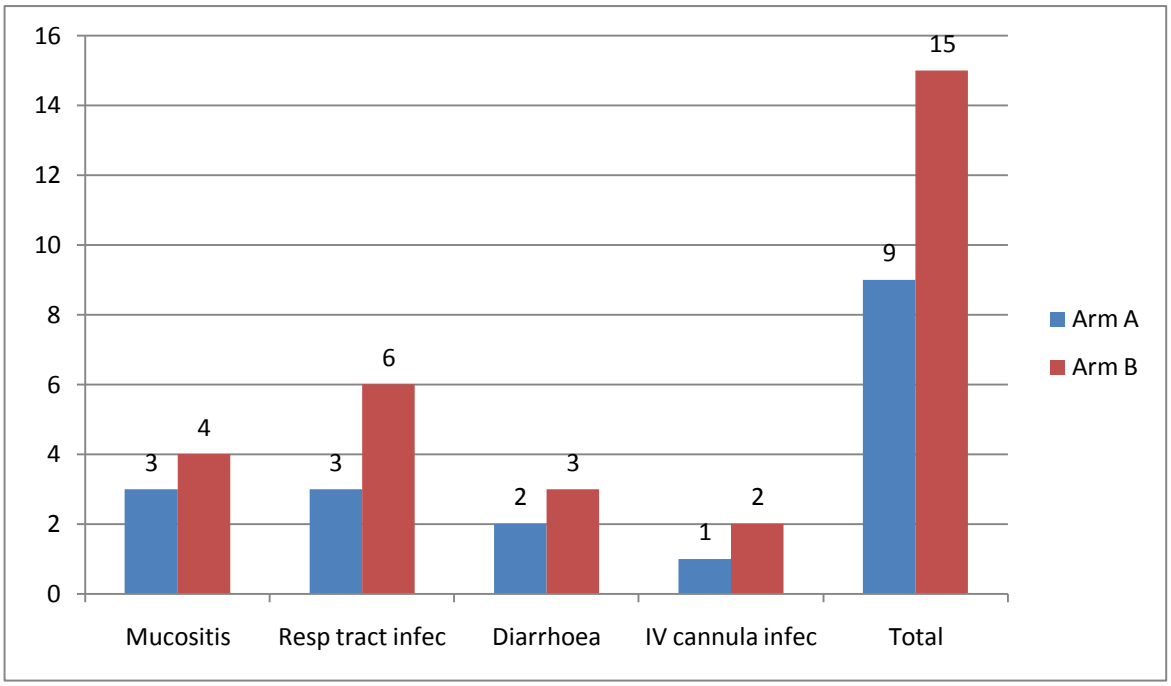


Figure 8 : Clinically documented infection (Probable)



DISCUSSION

Our study evaluated the role of primary prophylaxis of antibiotics in post chemotherapy breast carcinoma patients. The incidence of febrile neutropenia in first cycle is considerably less in antibiotic group. Henri et al[6] noted 8.2% incidence of FN with FEC chemotherapy in breast carcinoma patients where as Gianni et al[52] noted 20% in paclitaxol-adriamycin combination chemotherapy.

Cullen et al[38] stated that there would be higher incidence of FN in first cycle than rest of the cycles. In his study with Levofloxacin prophylaxis in both solid tumours and lymphoma patients the incidence of FN was 3.8% in first where as it was 8% in rest of the cycles.. In our study incidence of FN in first cycle is 5.3% and 15% in antibiotic and placebo group and the incidence is less in subsequent cycles in both antibiotic and placebo group ie., 2.7% and 5.5%. The protective effect of antibiotic is 3 times more effective in first cycle and it is statistically significant where it is only 2 times in rest of the cycles which is also statistically significant .The declining trend of FN in subsequent cycles may be due to cytoreduction of tumour and improvement in immunity. The first cycle febrile neutropenia is more important, as more care and precautions would be taken for these group of patients in rest of the cycles . Prophylactic Gatifloxacin decreases the overall incidence of febrile neutropenia by more than 50%.

Analysing the incidence of FN in FEC combination chemotherapy separately it was 2.88% and 7.73% respectively in antibiotic and placebo groups respectively

where as the incidence quoted in PACS trial[6] was around 8.4% which was almost similar to our placebo group. In the same study with FEC 3 cycles followed by 3 cycles of Docetaxol , the incidence of FN was 11.2% where as David et [53] al had observed 16% incidence of FN in their study using Taxol-Epirubicin combination as neoadjuvant chemotherapy. In our study observed incidence of FN in TE combination chemotherapy was 5.12% and 3.33% in antibiotic and placebo groups which was not statistically significant. The lesser incidence of FN in TE subgroup could be attributed to lesser number of patients received TE. Thus our result could not be taken as a conclusive one.

The incidence of hospital admission in our study was 5.3% and 15.9% in antibiotic and placebo groups respectively in first cycle where as it was 2.76% and 5.53% in subsequent cycles. As the benefit of prophylactic antibiotics in decreasing febrile neutropenia was more in first cycle , similar benefit for hospital admission was seen in first cycle. Cullen et al[38] had observed , the incidence of hospital admission was 15.7% and 21.6% respectively in levofloxacin and placebo group respectively. Reduction in the incidence of hospitalisation by antibiotic was statistically significant in first cycle , where as it was not significant in subsequent cycles. Cullen et al [38] had stated that the risk reduction of hospitalisation is 36% in first cycle where as it was only 27% in subsequent cycles .Same results were also obtained by Heijnen et al [41] , on using roxithromycin and ciprofloxacin in small cell lung carcinoma patients , he had observed 17% and 31% incidence of hospitalisation with antibiotic and placebo groups respectively. Median days of hospital admission due to febrile neutropenia observed by the same authors was 4 and 5 days

respectively . But against this study , in our study median days of hospital admission was similar in both arms ie., 5 days . In this study there was almost 50% reduction of hospitalisation with prophylactic antibiotics across all cycles. Decrease in hospitalisation cuts the extra cost due to hospitalisation and also decreases the exposure to cross resistant organisms.

Clinically documented infections was observed in 9 out of 18 patients (50%) and 15 out of 41 patients (36.5%) in antibiotic and placebo groups respectively. Cullen et al [38] had observed the following infections upper respiratory tract 24.7%, lower respiratory tract 12.9%,skin (10.5%), and urinary tract (8.3%) in febrile neutropenia . Heijhen et al [41] in their study on the prophylactic role of antibiotics by using Ciprofloxacin and Roxithromycin had observed more clinical documentation of infection in placebo group than antibiotics group where as in our study it was antibiotic group which had more clinical documentation of infection. Also in their study incidence of respiratory and GIT infection was almost reduced to half in antibiotic group patients. Usually pneumonia in a neutropenic patients was associated with high mortality. In our study there was 50% decrease in respiratory tract infections in placebo group.

One patient had life threatening diarrhoea and three more patients had pneumonia requiring ICU admission in placebo group where as only one patient in antibiotic group had admission in ICU for pneumonia. So ICU admissions are reduced considerably in antibiotic group. Heijhen et al[41] in their study had

documented 6% and 2% ICU admission in placebo and antibiotic group respectively.Median number of ICU admission was 7 and 2 days where as in our study it was 4 days in both study groups. All the patients except one who had ICU admissions had grade IV neutropenia.

One of the main goal of antibiotic prophylaxis was to decrease the morbidity due to myelosuppression in elderly patients or patients with comorbids like systemic hypertension, ischemic heart disease , Diabetis mellitus etc. our study was a negative study which have not shown any benefit of antibiotic prophylaxis in patients with comorbids.But in elderly patients ie., age > 50 there was considerable reduction in the incidence of febrile neutropenia with antibiotics.

There was not much literature available on the role of antibiotic prophylaxis in concurrent chemoradiotherapy in breast carcinoma patients .Various studies mentions the incidence of dermal , haematological and cardiac toxicity was more in concurrent chemoradiotherapy than sequential therapy. Rouesse et al [54] in their study on adjuvant therapy in node positive breast cancer using sequential chemo-radiotherapy or concurrent chemo-radiotherapy observed the incidence of gradeIII \ IV neutropenia and febrile neutropenia was more in concurrent chemo-RT arm. In our study the incidence of FN was 4.71% and 8.16% in antibiotic and placebo arms respectively . The usage of antibiotic prophylaxis had decreased the incidence of febrile neutropenia by almost 50% in concurrent chemoRT .

Blood culture positivity documented in 18 and 41 febrile neutropenic patients in antibiotic and placebo groups in our study was 16.6%% and 9.7 % respectively where as Cullen et.al [38] in their study had documented culture positivity in 4.6% and 12.6% .Contrary to Cullen's study we had more culture positivity in antibiotic group. Out of the seven documented infection , 4 was gram negative where as 3 was gram positive. Kanamaru et al[55] in their study had mentioned commonest isolate from blood in febrile neutropenic patients was gram positive organisms ie., Staphylococcus species in 22% followed by Pseudomonas aeruginosa in 11.6% . In our study we had more gram negative than gram positive organisms. Commonest organism isolated is Streptococcus pyogenes followed by Klebsiella pneumonia and Esherichia coli. We had no documented fungal infection.

One of the main purpose of employing antibiotic prophylaxis to prevent febrile neutropenia in patients receiving chemotherapy is to decrease the incidence of infection related mortality. Most of the trials conducted have shown a decrease in infection related mortality in patients receiving anti biotic prophylaxis. Gafter et al[45] in his meta-analysis observed that fluoroquinolone prophylaxis reduced the risk for death by 48% (CI, 33% to 65%) and infection-related death by 62% (CI, 31% to 79%). Mario Cruciani [48] in his meta analysis comparing the benefit of addition of gram-positive prophylaxis to fluoroquinolone in neutropenic patients also found that antibiotic prophylaxis does decrease the mortality rate but found no significant effect of the addition of gram positive prophylaxis to quinolone in terms of infection related mortality. (RR, 0.95; 95% CI, 0.53 to 1.71). Reuter et al[44] in their prospective observational study observed a significantly higher rate of mortality(33%) on

discontinuation of levofloxacin when compared with that of routine fluroquinolone prophylaxis.(2.9%).Also w hen levofloxacin was reintroduced the mortality rate was comparable to those period of routine levofloxacin prophylaxis. In contrary in our study there was no infection related mortality in both the groups.

Limitations Of The Study

1. In this study , even though number of localised and metastatic disease patients in both arms were equal ,patients were not stratified by exact breast carcinoma staging.
2. No defined criteria for the use of colony stimulating factors ,mainly it was decided on the basis of treating phycisians discretion . It was not taken in to account for analysis.
3. Dose intensity of chemotherapy was not analysed.
4. It is possible some associations mentioned in this study may have occurred by chance. There is some possibility , unknown variables may have confounded the results.

Summary and Conclusion

This study is an attempt to assess the clinical evidence supporting the efficacy of antibiotic prophylaxis with fluoroquinolones in neutropenic cancer patients. 188 breast carcinoma patients were randomly assigned to treatment or observation group each consisting of 94 patients. Treatment group patients received Gatifloxacin 400 mg OD from day 6 to day 14 of each chemotherapy cycle**.** Patients who developed febrile neutropenia were admitted in the hospital and oral or IV antibiotics were administered based on age, PS and clinical picture of patients. Primary end points of the study were the number of febrile episodes, documented infection, culture positive infection, infection related mortality while the secondary end points of the study include number of febrile episodes in first and then subsequent cycles, days of hospitalisation , ICU admissions, requirement of intravenous antibiotics, isolation of organisms, whether antibiotic prophylaxis helpful in elderly or patients with comorbids.

- The incidence of febrile neutropenia in first cycle is considerably less in antibiotic group. The protective effect of antibiotic is 3 times more effective in first cycle and it is statistically significant where it is only 2 times in rest of the cycles which is not statistically significant. The incidence of hospital admission in our study was 5.3% and 15.9% in antibiotic and placebo groups respectively in first cycle where as it was 2.76% and 5.53% in subsequent cycles .In our study median days of hospital admission was similar in both arms ie., 5 days . In this study there was almost 50% reduction of hospitalisation with prophylactic antibiotics across all cycles. Clinically documented infections was observed in 9 out of 18 patients (50%) and 15

out of 41 patients (36.5%) in antibiotic and placebo groups respectively.One patient had life threatening diarrhoea and three more patients had pneumonia requiring ICU admission in placebo group where as only one patient in antibiotic group had admission in ICU for pneumonia. So ICU admissions are reduced considerably in antibiotic group.

Conclusions drawn from this study include

- Incidence of febrile neutropenia is decreased in patients who received gatifloxacin and this effect was seen considerably more in the first cycle of chemotherapy than the subsequent cycles.
- Incidence of hospitalization due to febrile neutropenia was also less in patients receiving antibiotic prophylaxis .However median duration of hospitalization of patients remained the same irrespective of antibiotic prophylaxis or not.
- Antibiotic prophylaxis also reduced the need of intravenous antibiotics in patients with febrile neutropenia.
- Clinically and microbiologically documented infection was not decreased with the use of antibiotic prophylaxis
- Antibiotic prophylaxis did not exert additional positive effect in patients with comorbid condition and in patients with metastatic disease.

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PROFORMA

Name: **Stage**

OP No: **T** - 1 / 2 /3
/4

Index No: **N**- 1 / 2 /3

Age : **M**- 0 / 1

Sex: **ER** – 1 / 2

PS: **Ht:** **Wt:** **BSA :** **PR** – 1 / 2

I. COMORBIDS **HER** – 1 / 2

1. HT - 1 / 2 **GRADE**- 1 / 2
/ 3

2. DM 1 / 2 **NEOADJ / ADJ CT**

3. IHD 1 / 2 **CT SCHEDULE** – (FEC, TE) – 1 / 2 / 3

4. Others **CONCURR CT /RT** – 1 / 2

1st Cycle – Date

Nadir TC Hos Admn: 1 / 2 Fever: 1 /
2

ICU – 1 / 2 Pneumonia : 1 / 2 Hypoten : 1 / 2
Others:

ORAB/ IVAB – 1 / 2 IInd line AB – 1 / 2 Days of AB:
Days of Admn:

2nd Cycle – Date

Nadir TC Hos Admn: 1 / 2 Fever: 1 /
2

ICU – 1 / 2 Pneumonia : 1 / 2 Hypoten : 1 / 2
Others:

ORAB/ IVAB – 1 / 2 IInd line AB – 1 / 2 Days of AB:
Days of Admn:

3rd Cycle – Date

Nadir TC Hos Admn: 1 / 2 Fever: 1 / 2

ICU – 1 / 2 Pneumonia : 1 / 2 Hypoten : 1 / 2
Others:

ORAB/ IVAB – 1 / 2 IInd line AB – 1 / 2 Days of AB:
Days of Admn:

4th Cycle – Date

Nadir TC Hos Admn: 1 / 2 Fever: 1 / 2

ICU – 1 / 2 Pneumonia : 1 / 2 Hypoten : 1 / 2
Others:

ORAB/ IVAB – 1 / 2 IInd line AB – 1 / 2 Days of AB:
Days of Admn:

5th Cycle – Date

Nadir TC Hos Admn: 1 / 2 Fever: 1 / 2

ICU – 1 / 2 Pneumonia : 1 / 2 Hypoten : 1 / 2
Others:

ORAB/ IVAB – 1 / 2 IInd line AB – 1 / 2 Days of AB:
Days of Admn:

6th Cycle – Date

Nadir TC Hos Admn: 1 / 2 Fever: 1 / 2

ICU – 1 / 2 Pneumonia : 1 / 2 Hypoten : 1 / 2
Others:

ORAB/ IVAB – 1 / 2 IInd line AB – 1 / 2 Days of AB:
Days of Admn: